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Prediction-driven matched molecular pairs to interpret QSARs and aid the molecular optimization process

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Abstract

© 2014 Sushko et al.; licensee Springer. Background: QSAR is an established and powerful method for cheap in silico assessment of physicochemical properties and biological activities of chemical compounds. However, QSAR models are rather complex mathematical constructs that cannot easily be interpreted. Medicinal chemists would benefit from practical guidance regarding which molecules to synthesize. Another possible approach is analysis of pairs of very similar molecules, so-called matched molecular pairs (MMPs). Such an approach allows identification of molecular transformations that affect particular activities (e.g. toxicity). In contrast to QSAR, chemical interpretation of these transformations is straightforward. Furthermore, such transformations can give medicinal chemists useful hints for the hit-to-lead optimization process. Results: The current study suggests a combination of QSAR and MMP approaches by finding MMP transformations based on QSAR predictions for large chemical datasets. The study shows that such an approach, referred to as prediction-driven MMP analysis, is a useful tool for medicinal chemists, allowing identification of large numbers of "interesting" transformations that can be used to drive the molecular optimization process. All the methodological developments have been implemented as software products available online as part of OCHEM (http://ochem.eu/). Conclusions: The prediction-driven MMPs methodology was exemplified by two use cases: modelling of aquatic toxicity and CYP3A4 inhibition. This approach helped us to interpret QSAR models and allowed identification of a number of "significant" molecular transformations that affect the desired properties. This can facilitate drug design as a part of molecular optimization process.

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Keywords

Interpretation, Inverse QSAR, Matched molecular pairs, Medicinal chemistry, MMP, Molecule optimization, OCHEM, Online chemical modelling environment, QSAR